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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,265	11/04/2003	Brenda F. Baker	ISIS-5300	7033

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EXAMINER	
PITRAK, JENNIFER S	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
02/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/701,265	BAKER ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *120,121,124-128,131-133,136-154 and 157-167* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *120, 121, 124, 127, 136-140, 143, 148, and 149* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/06/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 125,126,128,131-133,141,142,144-147,150-154 and 157-167.

DETAILED ACTION

Remarks

Claims 125, 126, 128, 131-133, 141, 142, 144-147, 150-154, and 157-167 are withdrawn from consideration because they are directed to non-elected subject matter. In the amendments filed 07/09/2008, claim 120 was amended. Claims 120, 121, 124, 127, 136-140, 143, 148, and 149 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Terminal Disclaimer

The terminal disclaimers filed on 12/04/2008 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patents 6,107,094 and 5,898,031 and Application No. 09/479,783 have been reviewed and are accepted. The terminal disclaimers have been recorded.

Double Patenting - Rejections Withdrawn

The filing of the terminal disclaimers on 12/04/2008 has obviated the rejection of claims 139, 140, 143, 148, and 149 on the ground of nonstatutory obviousness-type double patenting over claims 4, 7, and 8 of U.S. Patent No. 6,104,094 and over claim 29 of U.S. Patent 5,898,031. Therefore, the rejections are withdrawn.

The filing of the terminal disclaimers on 12/04/2008 has obviated the provisional rejection of claims 120, 121, 124, 127, and 136-138 on the ground of nonstatutory obviousness-

type double patenting over claims 333-359 of copending Application No. 09/479,783. Therefore, the provisional rejection is withdrawn.

Claim Rejections - 35 USC § 103 - NEW

Claims 120, 121, 124, 127, 136-140, 143, 148, and 149 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee, *et al.* (Cell 1993, vol. 75, pages 843-854), Manche, *et al.* (Molecular and Cellular Biology 1992, vol. 12, pages 5238-5248), Agrawal, *et al.* (WO 94/01550, item 269 on 04/04/2005 IDS) and Baracchini, *et al.* (US 5,801,154).

The claims are directed to compositions comprising a duplex of non-linked strands 17 to 25 linked nucleotides in length wherein each strand is a gapmer comprising a gap of at least 4 nucleosides comprising a 2'-OH and wings comprising 2'-OCH_3 modifications.

At the time the invention was made short duplex RNAs with complementarity to a gene were known to those of ordinary skill in the art and were synthesized for a variety of purposes such as study of enzyme structure and regulation of gene expression.

Lee, *et al.* teach that lin-4 is a gene essential for the normal temporal control of postembryonic developmental events in *C. elegans* that acts by negatively regulating the level of LIN-14 protein. Lee, *et al.* further teach that the lin-4 gene transcribes two different products, one of which forms a stem-loop duplex structure with imperfect complementarity with lin-14 mRNA, suggesting that lin-4 regulates lin-14 translation via an antisense RNA-RNA interaction. Lee, *et al.* do not teach duplexes with perfect complementarity to a gene and do not teach the use of modified nucleotides such as 2'-OCH_3.

Manche, *et al.* teach that the protein kinase DAI, the double-stranded RNA-activated inhibitor of translation, is a pivotal cellular regulatory enzyme that is an important element in the

host antiviral response. Despite its importance as a regulatory enzyme, the interactions between DAI and its RNA effectors were complicated and incompletely understood. To better understand these interactions Manche, *et al*. analyzed interaction of the enzyme with RNA duplex molecules of specified sizes ranging from 15-104 nt (see figure 1) in order to study binding and protection of dsRNA as well as activation and inhibition of the kinase.

Agrawal, *et al*. teach self-stabilized oligonucleotides comprising a target-hybridizing region and a self-complementary region. On page 15, Agrawal, *et al*. teach that the self-complementary region of the oligonucleotide is fully or partially complementary to the hybridizing region while at page 9, line 30 through page 10 line 1 they teach that the target hybridizing region is complementary to a nucleic acid sequence from a variety of sources including viruses, pathogens, cellular genes or gene transcripts. On page 8 Agrawal, *et al*. teach that the self-stabilized oligonucleotides are composed of ribonucleotides, deoxynucleotides and/or modified nucleotides. Page 15 and 16 describe embodiments where the oligonucleotide is a single nucleic acid strand that forms a double stranded structure as well as an embodiment where the self-complementary region is connected to the hybridizing region by a non-nucleotide linker, making the self-complementary region and the hybridizing region two separate complementary nucleic acid strands. On pages 17, line 27 through page 18 Agrawal, *et al*. teach that the self-stabilized oligonucleotides can be administered to the cells of an animal to inhibit gene expression in the animals.

At the time the instant application was filed those of ordinary skill in the art were familiar with antisense oligonucleotides used for research purposes and for inhibition of gene expression. The teachings of Baracchini, *et al*. are representative of knowledge of modified nucleic acids from the antisense art. Although it is acknowledged that antisense oligonucleotides inhibit

expression via a different mechanism, Baracchini, *et al.* provide a template of known modifications and screening methods that form a basis for stabilization of duplex RNA structures. Baracchini, *et al.* teach that preferred oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition and that such modifications are desirable in antisense oligonucleotides because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. One particular type of modified oligonucleotide described at column 8 is chimeric oligonucleotides, including gapmers.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make short duplex RNAs that comprise modified nucleotides and would have been further obvious to make these RNAs with differing numbers of the instantly claimed 2'-OCH_3 in each strand and to produce these modifications in a gapmer pattern. Lee, *et al.* and Agrawal, *et al.* teach inhibition via duplex RNAs and Manche, *et al.* teach that short duplex RNAs had uses in the study of enzyme binding. Based on the knowledge available to the person of ordinary skill of the ways to incorporate modified nucleotides (including gapmer structures) and the usefulness of modified nucleotides in providing nuclease stability and binding affinity that is provided by the antisense art, the person of ordinary skill would be motivated to use these known modifications and modification patterns as a starting point for optimizing the stability and affinity of short duplex RNAs. The person of ordinary skill in the art would be able to predictably make duplex RNA sequences comprising the claimed modifications because these modifications are well known and routinely used by those in the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak
Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635